

## STEREOSPECIFIC SYNTHESIS OF ENAMINES FROM $\alpha,\beta$ -EPOXYSILANES

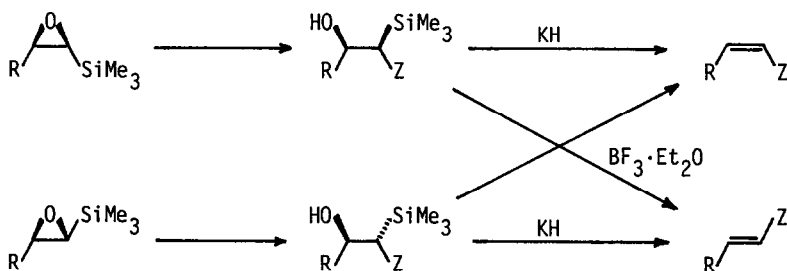
Paul F. Hudrlik,\* Anne M. Hudrlik, and Ashok K. Kulkarni

Department of Chemistry, Howard University  
Washington, D. C. 20059

**Abstract:** Isomerically pure cis and trans enamines were prepared from  $\alpha,\beta$ -epoxysilanes by alumina-assisted ring opening with pyrrolidine and morpholine followed by  $\beta$ -elimination.

Enamines are compounds of considerable synthetic importance.<sup>1</sup> However, the effect of stereochemistry on their reactions has been little studied, and few methods for their stereospecific synthesis exist.<sup>2,3</sup>

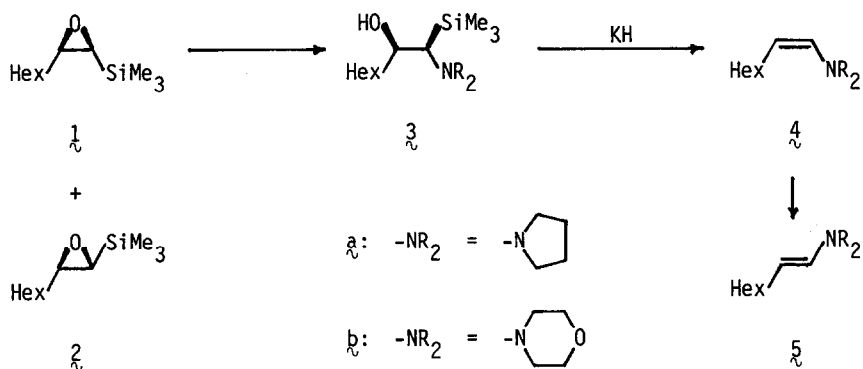
Several years ago, we reported a new, potentially general method for the stereospecific synthesis of heteroatom-substituted olefins.<sup>4</sup> This method is based on the finding that  $\alpha,\beta$ -epoxysilanes undergo regio- and stereospecific  $\alpha$  opening by a variety of reagents to produce diastereomerically pure  $\beta$ -hydroxysilanes,<sup>4,5</sup> and that these  $\beta$ -hydroxysilanes undergo stereospecific syn or anti  $\beta$ -elimination reactions under basic or acidic conditions, respectively.<sup>5a,6</sup>  $\alpha,\beta$ -Epoxy-silanes were thus termed "stereospecific vinyl cation equivalents".<sup>4</sup> We



have been interested in probing the scope and limitations of this method, and report here an application to the stereospecific preparation of simple pyrrolidine and morpholine enamines. This work demonstrates that the epoxysilane method can be used for the stereospecific synthesis of electron-rich, extremely acid sensitive olefins.

Initially, we attempted ring opening reactions of  $\alpha,\beta$ -epoxysilanes with amines under a variety of conditions and found the reactions to be sluggish.<sup>7</sup> Posner and Rogers reported that Woelm 200 neutral alumina catalyzes ring opening of epoxides by amines (and by other types of compounds).<sup>8</sup> Using alumina, we found that the cis epoxide **1**<sup>4</sup> undergoes clean ring opening with pyrrolidine and morpholine, although under more rigorous conditions. The trans epoxide **2**<sup>4</sup> was found to be inert to these conditions. Thus (as discussed below), a cis-trans mixture of epoxides can be used for the preparation of isomerically pure enamines.

An 86:14 mixture of epoxides  $\underline{1}$  and  $\underline{2}$ , prepared from heptanal and chloromethyl(trimethylsilyl)lithium,<sup>9</sup> reacted in the presence of alumina (in dioxane) with pyrrolidine (85°C, 96 h) and with morpholine (100°C, 24 h) to form the  $\alpha$ -amino- $\beta$ -hydroxysilanes  $\underline{3a}$ <sup>10</sup> and  $\underline{3b}$ ,<sup>10</sup> respectively. The  $\beta$ -hydroxysilanes were separated from the unreacted trans epoxide by fractional evaporative distillation,<sup>11</sup> and were obtained in 63.5% ( $\underline{3a}$ ) and 62% ( $\underline{3b}$ ) yields (not corrected for the fact that only the cis epoxide reacted). Their structures were confirmed by the downfield shift of the  $\beta$  protons in the NMR spectra of their derived acetates, and by their  $\beta$ -elimination reactions (below).



Our initial attempts to prepare cis enamines by KH-induced syn  $\beta$ -elimination reactions of  $\beta$ -hydroxysilanes  $\underline{3a}$  and  $\underline{3b}$  led to the trans isomers,  $\underline{5a}$  and  $\underline{5b}$ , or to cis-trans mixtures. We found that this was due to extremely facile acid-catalyzed cis-trans isomerization, and eventually were able to isolate the pure cis enamines  $\underline{4a}$  and  $\underline{4b}$  by carrying out all operations in glassware washed with aqueous NaOH. Isomeric purities were determined by NMR spectra taken in cyclohexane. (We were unable to separate the isomers by VPC.) Cis-trans isomerization was shown (for  $\underline{4b}$ ) to take place slowly in  $\text{CCl}_4$  and rapidly in the presence of  $\text{CHCl}_3$ . With  $\underline{4a}$ , isomerization was even more rapid.

Thus,  $\beta$ -hydroxysilane  $\underline{3a}$  was treated with KH in THF under nitrogen (room temperature, 2 h), the liquid was separated (no aqueous workup), and the solvent was removed under vacuum, to give the isomerically pure cis enamine  $\underline{4a}$ .<sup>12</sup> The trans isomer ( $\underline{5a}$ ) was not detectable by NMR (cyclohexane). Evaporative distillation gave 74% of a mixture of cis and trans enamines,  $\underline{4a}$  and  $\underline{5a}$  ( $\sim 2:3$  by NMR).<sup>13</sup> Pure trans enamine  $\underline{5a}$ <sup>10,12,14</sup> was obtained (78% yield) from a similar reaction in which the glassware had not been base washed.

Similarly,  $\beta$ -hydroxysilane  $\underline{3b}$  was treated with KH in THF, yielding cis morpholine enamine  $\underline{4b}$ <sup>10,12,13</sup> in 84% yield after evaporative distillation (no isomerization). A reaction in which the glassware had not been base washed gave a mixture of cis and trans enamines in 93% yield; after standing at room temperature this mixture isomerized to the pure trans enamine  $\underline{5b}$ .<sup>10,12</sup>

Only a few examples of simple cis enamines which are capable of isomerization to the trans isomers have previously been reported;<sup>2b,3</sup> these compounds have been found to be very unstable.<sup>15</sup> The fact that highly sensitive cis enamines can be prepared by  $\beta$ -elimination reactions of  $\beta$ -hydroxysilanes demonstrates the mildness and versatility of these reactions. The fact that an isomerically pure enamine can be obtained from a cis-trans mixture of epoxy-silanes is also noteworthy.<sup>16</sup>

Acknowledgments: We thank the National Science Foundation for support of this work, and we thank Dr. Robert J. Rona for useful discussions.

#### References and Notes

- For a comprehensive review of enamines, see P. W. Hickmott, *Tetrahedron*, **38**, 1975-2050, 3363-3446 (1982).
- Two methods for the stereospecific synthesis of enamines have been reported.
  - Diastereomeric mesitoate esters of amino alcohols (resulting from the reactions of cis- and trans-stilbene oxide with morpholine) were each treated with  $KOtBu$  in DMSO to give Z (pure) and E (75% E) trisubstituted enamines, respectively: M. E. Munk and Y. K. Kim, *J. Org. Chem.*, **30**, 3705-3710 (1965).
  - A number of cis and trans primary enamines have been prepared by retro-Diels-Alder reactions: J. L. Ripoll, H. Lebrun, and A. Thuillier, *Tetrahedron*, **36**, 2497-2503 (1980).
- Base-catalyzed isomerizations of allylamines to enamines have been shown to generate predominantly cis enamines; in some cases cis enamines in up to ~90% purity have been isolated. (a) J. Sauer and H. Prah1, *Tetrahedron Lett.*, 2863-2866 (1966); (b) J. Sauer and H. Prah1, *Chem. Ber.*, **102**, 1917-1927 (1969); (c) M. Rivière and A. Lattes, *Bull. Soc. Chim. Fr.*, 2539-2545 (1967); (d) M. Rivière and A. Lattes, *Bull. Soc. Chim. Fr.*, 4430-4435 (1968); (e) M. Rivière and A. Lattes, *Bull. Soc. Chim. Fr.*, 730-736 (1972); (f) A. J. Hubert, *J. Chem. Soc. C*, 2048-2050 (1968). See also (g) G. Rauchschwalbe and H. Ahlbrecht, *Synthesis*, 663-665 (1974); (h) H. Ahlbrecht and J. Eichler, *Synthesis*, 672-674 (1974); (i) H. Ahlbrecht and C. S. Sudheendranath, *Synthesis*, 717-719 (1982).
- P. F. Hudrlik, A. M. Hudrlik, R. J. Rona, R. N. Misra, and G. P. Withers, *J. Am. Chem. Soc.*, **99**, 1993-1996 (1977).
- (a) P. F. Hudrlik, D. Peterson, and R. J. Rona, *J. Org. Chem.*, **40**, 2263-2264 (1975); see also (b) A. P. Davis, G. J. Hughes, P. R. Lowndes, C. M. Robbins, E. J. Thomas, and G. H. Whitham, *J. Chem. Soc. Perkin I*, 1934-1941 (1981).
- P. F. Hudrlik and D. Peterson, *J. Am. Chem. Soc.*, **97**, 1464-1468 (1975).
- R. J. Rona, Ph.D. Thesis, Rutgers University, New Brunswick, N. J., 1978. See also J. J. Eisch and J. E. Galle, *J. Org. Chem.*, **41**, 2615-2621 (1976).
- G. H. Posner and D. Z. Rogers, *J. Am. Chem. Soc.*, **99**, 8208-8214 (1977); for a review, see G. H. Posner, *Angew. Chem., Int. Ed. Engl.*, **17**, 487-496 (1978).
- C. Burford, F. Cooke, E. Ehlinger, and P. Magnus, *J. Am. Chem. Soc.*, **99**, 4536-4537 (1977); C. Burford, F. Cooke, G. Roy, and P. Magnus, *Tetrahedron*, **39**, 867-876 (1983).
- The IR, NMR, and mass spectra were in agreement with the structure of this compound.

11. A preliminary experiment suggests that the  $\alpha$ -amino- $\beta$ -hydroxysilane  $3a$  and the trans epoxide  $2$  can be separated by extraction with dilute acid.
12. To ascertain the stereochemical purity of the enamines, the most useful peaks in the NMR spectra were those of the olefinic hydrogens  $\alpha$  to nitrogen:  $4a$ ,  $\delta$  5.68 (d,  $J$  = 9 Hz);  $5a$ ,  $\delta$  6.02 (d,  $J$  = 13.5 Hz);  $4b$ ,  $\delta$  5.41 (d,  $J$  = 8.5 Hz);  $5b$ ,  $\delta$  5.73 (d,  $J$  = 14 Hz). For additional NMR data on other cis and trans enamines, see ref 3b.
13. Treatment of this compound with 2,4-DNP reagent gave the expected 2,4-DNP of octanal, mp 103-105°C (lit. mp 106°C: R. L. Shriner, R. C. Fuson, D. Y. Curtin, and T. C. Morrill, "The Systematic Identification of Organic Compounds", 6th ed, Wiley, New York, N. Y., 1980, p 537).
14. Compound  $5a$  (stereochemistry not indicated, but presumably trans) has been reported: H. J. Jakobsen, S.-O. Lawesson, J. T. B. Marshall, G. Schroll, and D. H. Williams, J. Chem. Soc. B, 940-946 (1966).
15. Cis enamines with additional conjugating substituents (such as those with the nitrogen in an aromatic ring) or in some cases with the nitrogen in a ring containing additional heteroatoms appear to be considerably more stable than the simple cis enamines reported here. For examples, see (a) R. L. Stern and J. G. Krause, J. Org. Chem., **33**, 212-215 (1968); (b) M. G. Ahmed, S. A. Ahmed, and P. W. Hickmott, J. Chem. Soc. Perkin I, 2383-2386 (1980); (c) P. C. Bélanger, J. G. Atkinson, C. S. Rooney, S. F. Britcher, and D. C. Remy, J. Org. Chem., **48**, 3234-3241 (1983).
16. We have shown that water/acid can selectively open the cis epoxide in a cis-trans mixture (P. F. Hudrlik, R. H. Schwartz, and A. K. Kulkarni, Tetrahedron Lett., 2233-2236 (1979), footnote 14). Preliminary experiments indicate that methanol/alumina and thiophenol/alumina also react with the cis epoxide much faster than with the trans, indicating the potential for preparing isomerically pure enol ethers or vinyl sulfides from a cis/trans mixture of  $\alpha,\beta$ -epoxysilanes.

(Received in USA 8 October 1984)